EFFECT OF SOMATOSTATIN ANALOG ON PEPTIDE RELEASE AND TUMOR GROWTH IN THE ZOLLINGER-ELLISON SYNDROME

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The clinical presentation of Zollinger-Ellison syndrome (ZES) is the result of gastrin hypersecretion and may be modified by secondary peptide hypersecretion. Treatment is medical (H_2-blockers) or surgical (tumor excision and total gastrectomy). H_2-blocker escape occurs up to 23 per cent and surgical mortality ranges to 15 per cent. Treatment of advanced disease has limited success. Sandostatin® (SMS 201-995) has been shown to decrease basal gastrin and gastric acid secretion in ZES. We hypothesized that SMS would suppress basal and provoked gastrin and secondary peptide secretion in ZES. A patient with refractory, metastatic gastrinoma underwent provocative testing (test meal, calcium infusion, secretion bolus and tolbutamide bolus). Thirteen peptides were drawn at set intervals during these provocative tests. Testing was repeated during SMS therapy (100 micrograms subcutaneously three times per day). Gastrin, pancreatic polypeptide (PP) and glucagon levels were elevated at baseline. SMS suppressed all three peptides (mean 74 per cent) ($p<0.05$). Gastrin, PP and glucagon were provoked by all four tests (means above baseline, 19, 155 and 138 per cent, respectively). Gastrin-releasing peptide, gastric inhibitory peptide and insulin were provoked by calcium infusion (427, 306 and 162 per cent above baseline, respectively). SMS suppressed 14 of 15 of these peaked-provoked peptide levels (mean 72.5 per cent, $p<0.05$). Gastric analysis during calcium infusion showed SMS suppression of hourly gastric secretory volume by 77.5 per cent and of acid production (milliequivalents of acid) by 87.5 per cent. During a 20 month follow-up period, the patient was maintained on SMS, 200 micrograms subcutaneously three times per day. She has remained asymptomatic. Interval peptide profiles at two, eight and 18 months show normal gastrin, PP and glucagon levels. A computed tomographic scan at eight months shows a remarkable regression of primary and metastatic tumor. Regrowth, however, was noted at 19 months. SMS may be useful in ZES by suppressing basal and provoked gastrin and secondary peptide secretion and may occasionally give palliation by yielding temporary tumor registration.

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THE TREATMENT of gastrinoma has been controversial, although surgical treatment remains the primary therapy (1–5). Traditionally, surgical treatment consists of total gastrectomy (TG) with or without extirpation of the primary pancreatic tumor. Parietal cell vagotomy and intensive cimetidine therapy have also been advocated (6). Total gastrectomy carries a postoperative mortality rate of 5 to 15 per cent. In light of this mortality rate, primary medical management with H_2-blockers has been advocated (7). However, up to 23 per cent of the patients with gastrinoma have escaped from previously effective doses of cimetidine and ranitidine (2, 3, 5). These patients may subsequently undergo TG (3). The treatment of advanced gastrinoma has been difficult. Total gastrectomy remains palliative and debulking of metastatic deposits may provide temporary relief from excess gastrin. Chemotherapy, including streptozotocin or 5-fluorouracil, or both, provides limited benefit (8–10).

Somatostatin and octreotide acetate (SMS 201-995), an analog of native somatostatin (Sandostatin®), have been shown to inhibit peptide release from functional endocrine tumors (11–18). In patients with gastrinoma, SMS effectively suppresses serum gastrin levels and gastric acid secretion (11, 19–21). Gastrin provocation by a test meal or intravenous secretin is also suppressed by SMS (20). Reports of long term therapy of SMS are limited, but the results of one study demonstrated

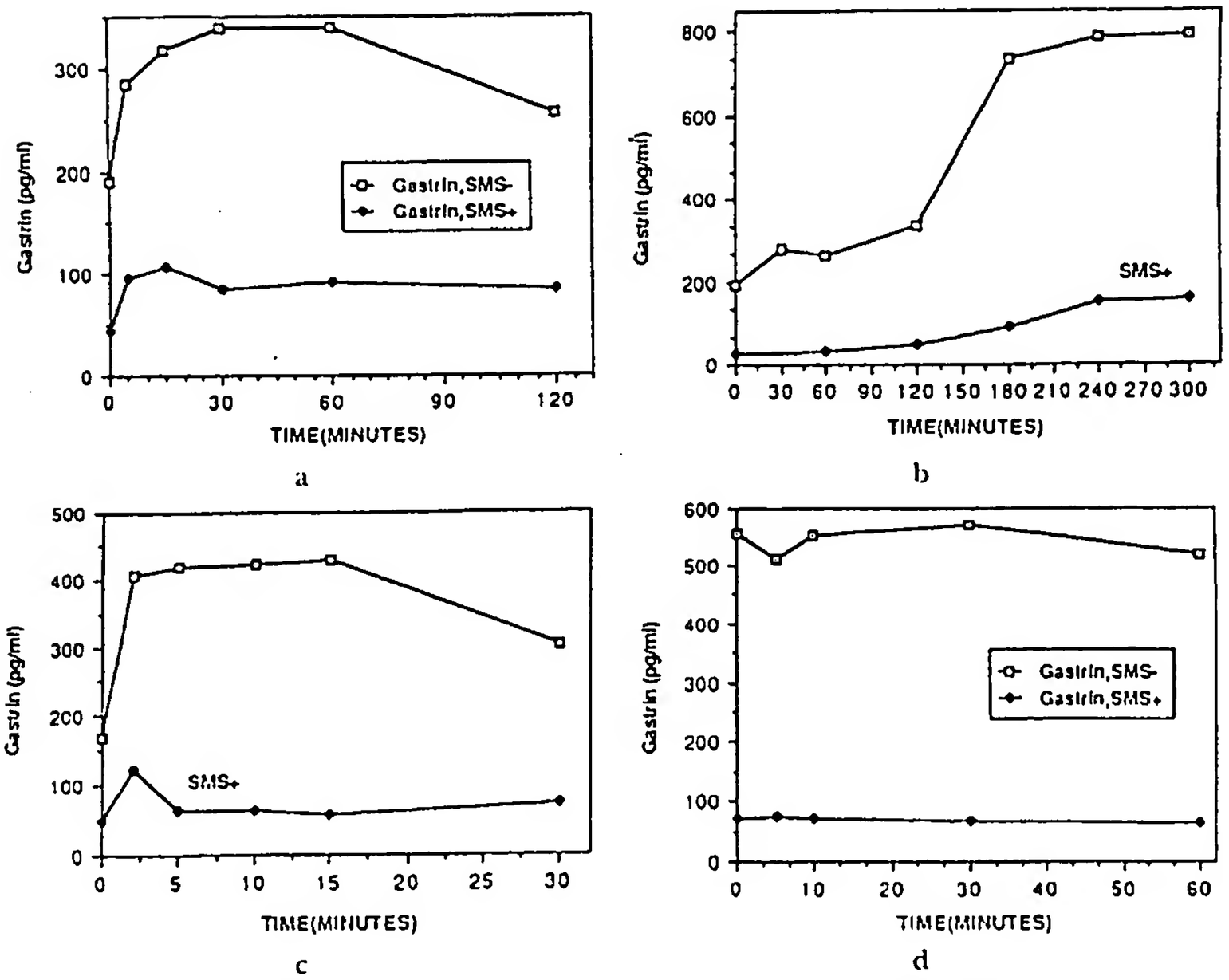

FIG. 1. Gastrin response before and after octreotide therapy; response to stimulation with test meal, a; a four-hour calcium infusion, b; a secretin bolus, c, and a tolbutamide bolus, d.

tumor regression in a patient with vasoactive intestinal polypeptide tumor (VIP-oma) (22). We have recently shown that gastrinomas, as well as other functional endocrine tumors of the pancreas, secrete secondary peptides. These peptides may have clinical significance. We hypothesized that SMS would suppress the basal and provoked levels of gastrin and secondary peptides from gastrinoma and would provide long term relief of symptoms by suppressing circulating gastrin levels. A patient with unresectable gastrinoma for whom intensive medical therapy failed was studied to determine the effect of SMS on circulating gastrin and secondary peptide levels. These peptide levels were measured in the basal (fasting) state and after provocation with a test meal, a calcium infusion, a secretin bolus and a tolbutamide bolus. Long term therapy with SMS controlled the gastrin levels, alleviated symptoms and was associated with a significant regression of tumor.

MATERIALS AND METHODS

Patient report. This 69 year old morbidly obese, hypertensive white woman with multiple endocrine neoplasia type I (MEN-I) and gastrinoma first presented to Oregon Health Sciences University in August of 1986. She had a lifelong history of intermittent watery diarrhea and epigastric pain. The diarrhea began in childhood and epigastric pain began in her teenage years. She has three brothers with MEN-I. The oldest underwent gastrectomy and parathyroidectomy. The second oldest had hyperparathyroidism and resection of a pancreatic tumor. The youngest had a pancreatic tumor as a solitary presentation. The epigastric pain of the patient led to cholecystectomy in 1978. At laparotomy, a duodenal ulcer was noted. The liver was reported as normal. She was subsequently treated with cimetidine until the pain, diarrhea, nausea and vomiting returned in 1983. A roentgenogram of the upper part of the gastrointestinal tract revealed a recurrent duodenal ulcer. An ultrasound in August 1983 showed a 1.5 centimeter lesion in the left hepatic lobe. Because of her strong family history of MEN-I, a full work-up was done in February 1984. Gastric analysis revealed an elevated basal acid output to maximal acid output ratio of 0.64, suggestive of the Zollinger-Ellison syndrome (ZES). The fasting plasma gastrin level was elevated at 491 picograms per milliliter. Endoscopy showed two active duodenal bulb ulcers, extensive duodenal scarring and diffuse gastritis. The results of specimens taken at biopsy were negative for malignant lesions. Ultrasound revealed progression of the hepatic mass. Computed tomography (CT) showed

TABLE I.—NORMAL PLASMA PEPTIDE LEVELS

Peptide	*Plasma level*
Insulin	<25 μU./ml.
C-peptide	<3.6 ngm./ml.
Gastrin	<100 pgm./ml.
Gastric inhibitory peptide	<400 pgm./ml.
Gastrin-releasing peptide	<500 pgm./ml.
Glucagon	25-250 pgm./ml.
Calcitonin	<100 pgm./ml.
Vasoactive intestinal peptide	<170 pgm./ml.
Substance-P	<100 pgm./ml.
Pancreatic polypeptide	<150 pgm./ml.
Neurotensin	<140 pgm./ml.
Motilin	<170 pgm./ml.
Somatostatin	<100 pgm./ml.

multiple hepatic defects. A biopsy of the liver was attempted but failed. Plasma parathyroid hormone was elevated. However, concomitant serum calcium levels were normal. No other endocrine abnormalities were identified. Surgical treatment was not advised because of her morbid obesity, hypertension and hepatic metastases. She was treated with a high dose (up to 600 milligrams taken orally every six hours) of cimetidine and Pro-Banthine® (propantheline bromide). She remained relatively asymptomatic until April 1986 when stool frequency increased to 15 to 20 bowel movements per day and abdominal pain returned. CT scans taken in July and August 1986 showed massive enlargement of the tumor, increased number of hepatic metastases and a 9 centimeter mass in the head of the pancreas and in the region of the porta hepatis. A specimen taken at repeat needle biopsy of the liver revealed metastatic gastrinoma. Plasma gastrin levels remained elevated at 425 picograms per milliliter. Alkaline phosphatase levels were elevated at 154 units per liter. Other liver function tests were within normal limits. In August 1986, the serum creatinine level was 2.2 milligrams per deciliter with a creatine clearance of 57 milliliters per minute. Treatment with 5-fluorouracil and streptozotocin was considered, but the nephrotoxicity of the latter drug precluded its use. She was referred to Oregon Health Sciences University for therapy with Sandostatin. On admission, the patient was an obese (357 pounds) woman in no distress. Other than signs of hypertension, the results of the physical examination were otherwise unremarkable. The abdominal examination was hindered by morbid obesity. Her medical history was significant for a subtotal thyroidectomy for goiter, at which time a single normal para-thyroid gland was removed. Hypertension was moderately well-controlled with Aldactone® (spironolactone).

Study protocol. The patient was admitted to the Clinical Research Center at the Oregon Health Sciences University for a nine day protocol. All medications were stopped. On each of the first four days, a provocative test was performed after an overnight fast. On day 5, SMS therapy was initiated at 100 micrograms subcutaneously three times a day and was continued throughout the rest of the testing period. Identical provocative tests were repeated during the last four days while on SMS therapy. Peptide profiles were drawn (15 milliliters of blood) at set times during each test day. The plasma peptide profiles included plasma insulin. C-peptide, gastric inhibitory peptide (GIP), gastrin-releasing peptide (GRP), glucagon, calcitonin, vasoactive intestinal peptide (VIP), substance-P, pancreatic polypeptide (PP), neurotensin, motilin, somatostatin (SRIF), and somatostatin analog (SMS). On days 1 and 6, the patient received a standard test meal (321 calories, 27 grams of carbohydrate, 15 grams of protein and 17 grams of fat). Peptide profiles were drawn at zero, 15, 30, 60 and 120 minutes. On days 2 and 7, the patient received a four-hour calcium infusion (15 milligrams per kilogram per day of elemental calcium). Peptide profiles were drawn at zero, 30, 60, 120, 180, 240 and 300 minutes. On days 3 and 8, the patient received a secretin bolus (2 clinical units per kilogram given intravenously, Kabi) and peptide profiles were drawn

TABLE II.—PROVOCATION AND SUPPRESSION OF CIRCULATING PEPTIDE LEVELS

Secondary peptide	*Baseline level, pgm./ml.*	*Suppression with SMS, per cent*	*Provocative test*	*Peak provoked level, pgm./ml.*	*Suppression with SMS, per cent*
Pancreatic polypeptide, N<150 pgm./ml.	1,251	70	Test meal	1,810	89
			Calcium	2,351	49
			Secretin	1,960	65.5
			Tolbutamide	1,650	83
Glucagon, N=25 to 250 pgm./ml.	352	68	Test meal	547	59
			Calcium	297	69
			Secretin	485	77
			Tolbutamide	632	25
Gastrin-releasing peptide, N<500 pgm./ml.	<200	—	Calcium	855	66.5
Gastric inhibitory peptide, N<400 pgm./ml.	169	—	Calcium	517	76
Insulin, N<25 μU./ml.	29.9	—	Calcium	48.6 μU./ml.	53

SMS, Somatostatin®.

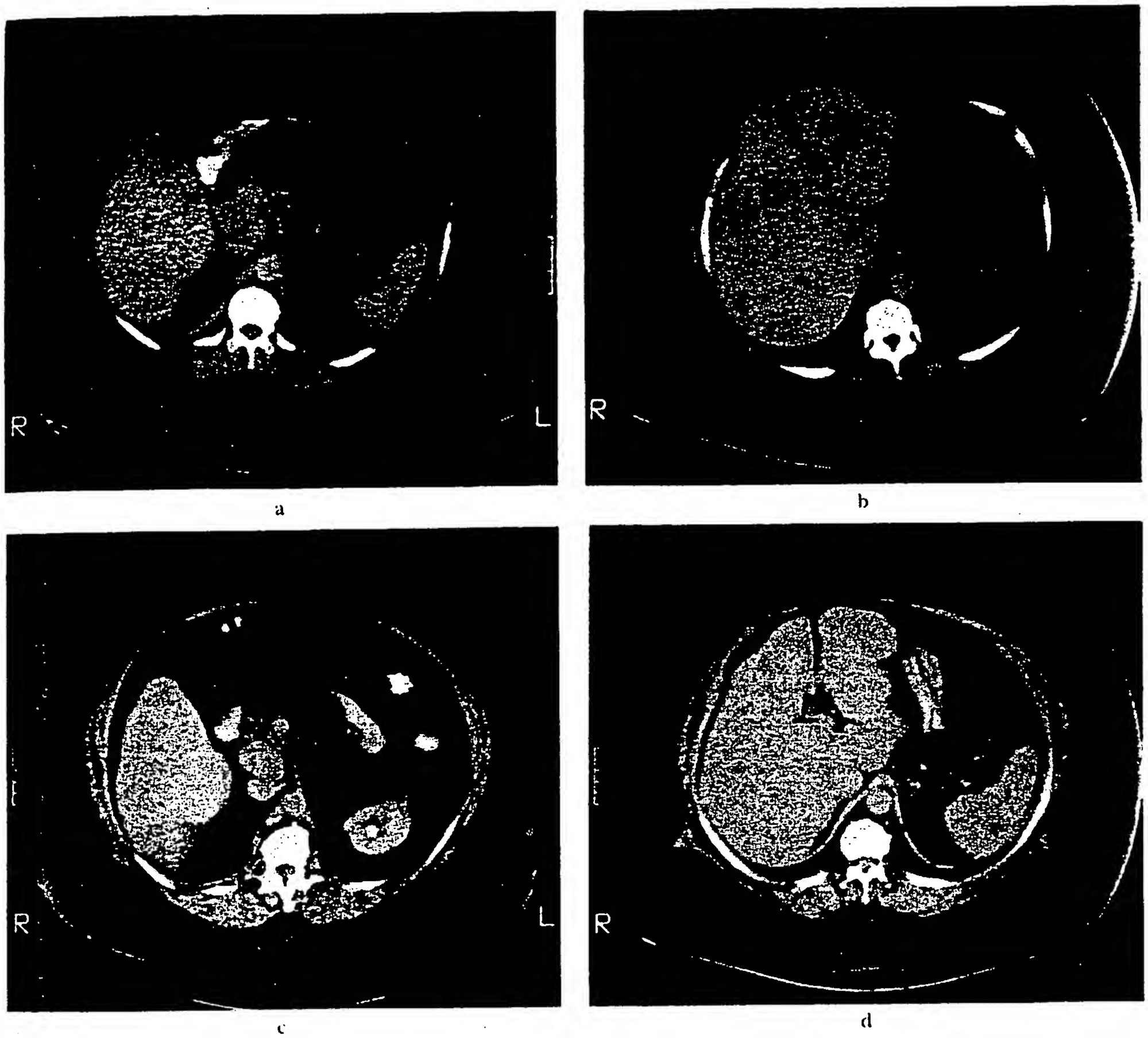

FIG. 2. Decrease in size of primary pancreatic tumor and hepatic metastases after treatment with SMS. a, Large mass in head of pancreas with compression of vena cava; b, multiple hepatic metastases; c, regression of pancreatic mass with reduction of vena cava compression, and d, regression of hepatic metastases.

at zero, two, five, ten, 15 and 30 minutes. On days 4 and 9, the patient received 1 gram bolus of tolbutamide given intravenously. Peptide profiles were drawn at zero, five, ten, 30 and 60 minutes. On days 2 and 7, during the calcium infusion, gastric analysis was performed on and off SMS. Gastric fluid was collected by way of a fluoroscopically placed nasogastric tube and hourly totals (up to five hours) analyzed for total volume, pH, milliequivalents of acid and milliequivalents of acid per liter. Based on the excellent response of the patient to SMS therapy, she was maintained on SMS 100 micrograms subcutaneously three times per day. Serum gastrin levels and peptide profiles have been subsequently drawn on a monthly basis.

The techniques of peptide radioimmunoassay (RIA) used in this study have been well characterized for gastrin (23), PP (24), VIP (25), motilin (26), neurotensin (27), substance-P (28), calcitonin (23), GIP (29), insulin (29), C-peptide (30) and GRP (31). Interassay and intra-assay coefficients of variation for each test ranged from 5 to 15 per cent. For each specific RIA, there is no cross-reactivity with any other peptide (including insulin and C-peptide). Normal plasma levels

TABLE III.—EFFECT OF SANDOSTATIN® ON GASTRIC ANALYSIS DURING CALCIUM INFUSION

	Calcium			*Calcium/SMS*		
Time, hr.	*Volume*	*mEq.*	*mEq./L.*	*Volume*	*mEq.*	*mEq./L*
1 . .	240	28	117	90	4	44
2 . .	240	27	113	20	1.3	67
3 . .	240	21	114	50	3.3	65
4 . .	170	19	111	40	3.2	80
5* .	35	2	68	80	4.8	60

*One hour after calcium infusion stopped. .

for each peptide have been established (Table I).

RESULTS

Baseline peptide levels. Of the 13 peptides measured, this patient demonstrated elevated baseline plasma levels of gastrin (N<100 picograms per milliliter), PP (N<150 picograms per milliliter) and glucagon (N=25 to 250 picograms per milliliter) (Table II). Sandostatin suppressed baseline gastrin levels by 83 per cent (278 to 46 picograms per milliliter) ($p<0.05$), PP by 70 per cent (1,251 to 373 picograms per milliliter) ($p<0.025$) and glucagon by 68 per cent (352 to 112 picograms per milliliter) ($p<0.05$).

Provoked gastrin levels. Of the 13 peptides measured, five were provocable (gastrin, PP, glucagon, GRP and GIP). Test meal values were not available for glucagon, GRP or GIP.

Plasma gastrin was provoked by all four tests (Fig. 1). After a test meal, plasma gastrin levels increased quickly to a plateau by 15 minutes and peaked at 340 picograms per milliliter by 30 minutes. Sandostatin blocked this provocation by 75.3 per cent (340 to 84 picograms per milliliter). During calcium infusion, plasma gastrin concentrations increased progressively to a maximum level of 791 picograms per milliliter at 300 minutes ($p<0.025$). SMS suppressed this curve dramatically, decreasing the maximum level by 80.2 per cent (791 to 157 picograms per milliliter). After a secretin bolus, plasma gastrin values rose quickly and peaked at 427 picograms per milliliter at 15 minutes. SMS blunted this response, suppressing the maximum gastrin level by 86.4 per cent (427 to 58 picograms per milliliter). After a tolbutamide bolus, plasma gastrin levels remained elevated, reaching a peak of 572 picograms per milliliter at 30 minutes. Sandostatin suppressed the entire curve, decreasing the maximum level by 88.2 per cent (572 to 68 picograms per milliliter).

Provoked secondary peptide levels. PP was provoked by a test meal and a secretin bolus, but less dramatically by a calcium infusion (Table II). A test meal stimulated PP to a maximum level of 1,810 picograms per milliliter ($p<0.05$). SMS decreased the peak provoked level by 89 per cent (1,810 to 205 picograms per milliliter). Calcium infusion stimulated PP to a maximum of 2,351 picograms per milliliter ($p<0.025$). The calcium-provoked maximum PP level was suppressed by 49 per cent (2,351 to 1,204 picograms per milliliter). Secretin bolus stimulated PP levels to a maximum of 1,960 picograms per milliliter ($p<0.025$). SMS suppressed the peak level by 65.5 per cent (1,960 to 677 picograms per milliliter) after a tolbutamide bolus, and the highest PP level was 1,650 picograms per milliter. Sandostatin blunted this maximum PP level by 83 per cent (1,650 to 282 picograms per milliliter). SMS suppression was significant ($p<0.05$) in all of the aforementioned tests.

Plasma glucagon was minimally provoked by a test meal, calcium and secretin (Table II). Plasma glucagon was provoked by a test meal to a maximum of 547 picograms per milliliter ($p<0.05$). Sandostatin decreased the peak level by 58 per cent (547 to 231 picograms per milliliter). A calcium bolus stimulated glucagon levels to a peak of 297 picograms per milliliter. This peak was suppressed by 69 per cent (297 to 93 picograms per milliliter). Secretin provoked glucagon to a high of 485 picograms per milliliter. SMS suppressed this level by 77 per cent (485 to 112 picograms per milliliter). After a tolbutamide bolus, plasma glucagon levels peaked at 632 picograms per milliliter ($p<0.025$). Somatostatin analog suppressed the peak level 25 per cent (632 to 158 picograms per milliliter).

GRP was provoked by calcium infusion, but not by secretin bolus (Table II). A calcium infusion provoked GRP to a maximum of 855 picograms per milliliter ($p<0.025$). SMS suppressed the peak by 66.5 per cent (855 to 286 picograms per milliliter).

GIP was stimulated by a calcium infusion to a maximum of 517 picograms per milliliter. SMS suppressed this maximum GIP level by 76 per cent (517 to 125 picograms per milliliter) (Table II).

Insulin was provoked by a calcium infusion to a maximum level of 48.6 microunits per milliliter. SMS suppressed this peak provoked level by 53 per cent (48.6 to 23.0 microunits per milliliter).

Gastric analysis. The results of a gastric analysis performed during calcium infusion are given in Table III. When comparing non-SMS treated versus SMS treated results during a four hour period, gastric secretory volume, milliequivalent of acid

production and milliequivalent per liter were decreased during each hour period. Average hourly volume was decreased by 77.5 per cent and the milliequivalents of acid produced were suppressed by 87.5 per cent. During the fifth hour, when the calcium infusion was discontinued, these values returned to nearly equal levels.

Long term follow-up study. The patient was maintained on SMS at 200 micrograms subcutaneously three times per day. She has been observed for 20 months. A CT scan performed February 1987 showed marked resolution of the primary and metastatic tumor (Fig. 2). Only two small, subtle low density areas were noted in the right hepatic lobe. The mass in the pancreatic head, although distinctly visible, was substantially smaller. Compression of the inferior vena cava also had resolved during the eight months of SMS therapy. Unfortunately, a subsequent CT scan 19 months after initiation of SMS therapy showed readvancement of the tumor. However, follow-up gastrin, PP and glucagon levels have all been within normal limits (Table IV). The stool frequency has dropped to one to two bowel movements per day and she has been free from pain.

TABLE IV.—PEPTIDE LEVELS DURING LONG TERM SANDOSTATIN® THERAPY

Months after study	*Gastrin, pgm./ml.*	*Pancreatic polypeptide, pgm./ml.*	*Glucagon, pgm./ml.*
2	70	282	101
8	106	194	202
18	72	107	186

DISCUSSION

The results of this study demonstrated that Sandostatin may be effective in both the short and long term management of patients with ZES. Sandostatin decreased baseline and provoked plasma levels of gastrin and secondary peptides. Throughout a 20 month follow-up period, the debilitating symptoms of this patient have been alleviated, gastrin levels have normalized and CT scans taken after therapy have showed a remarkable regression of the primary and metastatic tumor, although regrowth had begun by 19 months.

Sandostatin suppressed the baseline and provoked gastrin levels in this patient. Sandostatin is a long-acting, more potent analog of native somatostatin (SRIF). SRIF and its analogs have been shown to suppress circulating insulin, VIP, glucagon, calcitonin and serotonin from their respective functional endocrine tumors (11–19). In ZES, Sandostatin has been shown to decrease gastrin levels at baseline (11, 13–15, 32) and after provocation with a test meal or secretin (19, 32, 33). Simultaneous gastric analysis has shown a concomitant suppression of secretory volume and amount of acid by SMS (11, 13–15, 32).

Sandostatin suppression of baseline and provoked gastrin levels has important therapeutic implications. The morning fasting gastrin levels for this patient were normalized by SMS therapy. Doses given in the late evening may, therefore, protect against nocturnal acid hypersecretion. Although the half-life of Sandostatin is 120 minutes, it has been shown to suppress titratable gastric acid and decrease gastric output up to 18 hours after a single subcutaneous dose (19).

Calcium infusion elevated circulating gastrin levels over a four hour period and levels continued to rise for an hour after the infusion was stopped. SMS effectively blocked this response. This effect may be important in some patients with ZES who, like this patient, have MEN-I. Eighteen to 41 per cent of patients with ZES have MEN-I (1, 3, 34, 35). Parathyroid hyperplasia is the most frequent abnormality found in patients with MEN-I, and coexistent hyperparathyroidism in patients with ZES is present in 18 per cent (35). Resultant hypercalcemia, although not present in this patient, may act as a constant stimulus and elevate gastrin levels. Accordingly, parathyroidectomy has been shown to lower basal and maximal acid output, decrease fasting gastrin and, in one-third of the patients, induce secretin insensitivity (36). The potentially additive stimulatory effect of calcium on gastrin secretion may also be blocked by Sandostatin.

Sandostatin also completely suppressed gastrin provocation by a secretin bolus. Without SMS, this patient demonstrated this well-known paradoxical response (37, 38) with a rapid, significant rise in gastrin levels. *In vivo* this response may be deleterious. The paradoxic enhancement of secretin of gastrin levels may stimulate additional acid secretion during the postprandial period when secretin should normally yield a reduction of gastric acid production. These subsequent increases in gastric acid may, therefore, be blunted by SMS.

A test meal provoked a prolonged gastrin surge that continued for two hours. Acid production would, therefore, continue after the stomach has emptied. This prolonged gastric acid effect may result from paradoxical gastrin stimulation by the secretin that is released as chyme enters the duodenum. Again, SMS may ameliorate this abnormal response.

Gastric analysis during calcium stimulation dem-

onstrated suppression of both secretory volume and acid production. Suppression of acid and volume may not only alleviate the ulcer diathesis and pain, but also the often incapacitating diarrhea caused by large gastric outputs, hyperosmolarity and acidic damage to the intestinal mucosa.

Gastrinomas, like other functional endocrine tumors (39), secrete secondary peptides in excess. These tumors arise from endocrine precursor cells, which originate embryologically in the neural crest and, thus, may retain the pluripotential ability to secrete other peptides. The results of our study demonstrated that secondary peptides secreted from functional endocrine tumors are also provocable by standard testing and suppressible by SMS. This patient demonstrated fasting baseline hypersecretion of PP and glucagon. Both peptides were provoked by calcium and secretin. Furthermore, PP was stimulated by a test meal and tolbutamide. Sandostatin suppressed the baseline levels of both peptides (glucagon into normal limits). Although within normal limits at fasting baseline, GRP, GIP and insulin levels were provocable by a calcium infusion. The peak provoked levels of all these secondary peptides were suppressed by SMS therapy. The normal function of these peptides and their individual roles in a net observed physiologic effect are not fully elucidated, because of their complex endocrine, paracrine and neurocrine activities. Therefore, the coelaboration of secondary peptides suggests that the clinical signs and symptoms seen in patients with functional endocrine tumors may not be entirely the result of hypersecretion of the primary peptide, but actually are the result of a complex interplay of numerous peptides.

The effect of SMS suppression of secondary peptides is not entirely clear, and interpreting potential therapeutic benefit may be complicated. PP stimulates gastric acid secretion in dogs (40). Therefore, suppression of circulating PP by SMS may be beneficial. However, PP itself inhibits the stimulation of gastric secretion by gastrin (40). GRP is a potent stimulator of gastrin secretion (41), and suppression of GRP by SMS may further reduce gastrin levels. One might suspect that suppression of GIP, which inhibits acid secretion, would antagonize the desired effect of SMS. GIP, however, is a weak enterogastrone (42) and its suppression probably would not play a significant role in raising gastric acid secretion. Inhibition of glucagon and insulin probably does not affect gastric acid secretion.

The suppression of gastrin and secondary peptides by Sandostatin may be an important addition to the treatment of gastrinoma since optimal therapy has been controversial and the treatment of advanced, metastatic disease has been largely ineffective. The primary source of symptoms, morbidity and eventual mortality in patients with ZES is the effect of hypergastrinemia and not tumor bulk. Death caused by progressive tumor in one series was 17 per cent over-all and 25 per cent if metastases were present (43). These tumors are very slow growing and the over-all ten year survival rate is 42 to 50 per cent (34, 43, 44). Unlike some other functional tumors, gastrinoma is commonly malignant, and only 40 per cent are considered benign (1, 34). Metastases at the time of diagnosis are found in approximately 60 per cent of the patients studied (1, 34).

TG was advocated by Zollinger and Ellison in their original description (45) and has remained the mainstay of surgical treatment (1, 3–5, 46). Local excision or partial pancreatectomy has been advocated for localized disease (4, 5).

However, others believe that, since benign disease is frequently multiple (especially with MEN-I) and that malignant disease is frequently metastatic, excision of the tumor is rarely indicated (4). The mortality rate from TG has ranged up to 15 per cent (1, 4), but a cumulative review of 248 patients yielded a mortality rate of 5.6 per cent (1). This decreased to 2.4 per cent if emergent instances were excluded (1). These authors emphasize the necessity of preoperative stabilization. Other authors have advocated parietal cell vagotomy alone (6). The advent of H_2-blockers stimulated research advocating primary use of these agents (7).

However, high doses of cimetidine required for control have disturbing side effects, especially in men (46). Up to 37 per cent of men treated at these levels develop impotence or gynecomastia.

Moreover, 15 to 50 per cent of the patients successfully treated with cimetidine or ranitidine, or both, such as this patient, have escaped from clinical control. Most of the patients for whom medical therapy fails ultimately undergo TG (2, 3, 47). Other patients have medical contraindications to surgical treatment or may refuse operation, and somatostatin may offer these patients an important alternative.

Long term therapy has been successful in controlling the symptoms and gastrin levels in this patient. Most remarkable is the dramatic regression of tumor. The results of other studies have shown an effect of SMS on tumor growth. This has included peptide-secreting tumors (adenoma

of the pituitary gland [48, 49], insulinoma [50] and VIP-oma [22], hormone sensitive tumors, such as carcinoma of the breast [51]), and other tumors (carcinoma of the pancreas [48] and chondrosarcoma [50]). The biochemical basis of this effect is unclear. Somatostatin may block a trophic effect of other gastroenteropancreatic peptides on the tumor. We have shown *in vitro* that SMS suppresses gastrin release or synthesis, or both, in acutely dispersed gastrinoma cells (unpublished observation). Blockade of gastrin release could theoretically lead to intracellular accumulation of gastrin granules and, ultimately, to cell death. Alteration of these processes may affect cell division or lead to cell death. Alternatively, Sandostatin suppression of synthesis, the finding of somatostatin receptors at the nucleus (52) and a study showing the inhibition of centrosomal separation by SMS (53) infer a direct effect upon the nucleus.

Although the observation of tumor regression in this patient offers a provocative insight into the mechanism of somatostatin action, it will probably occur in a minority of patients treated with this agent. Although tumor regression was temporary, it may have contributed to effective palliation. We do not, however, propose somatostatin analog as an antineoplastic drug.

SUMMARY

SMS suppresses baseline and provoked primary and secondary peptide secretion in patients with ZES. The effect of Sandostatin on secondary peptides may contribute to the therapeutic response. Long term therapy has been associated with regression of tumor and may contribute to palliation. Sandostatin may be used as a primary therapy in patients with ZES who have medical contraindications to surgical treatment, may be used to stabilize patients prior to operation (thus lowering the operative mortality rate) and may be used as an alternative therapy in those patients for whom medical or surgical treatment have failed.

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URINARY STONE FORMATION IN PATIENTS WITH CROHN' S DISEASE. R.Caudarella,°L.Pironi,E.Rizzoli,N.Malavolta,G.Martelli,•M. Miglioli and °L.Barbara. Ist.Patologia Medica e Medicina del Lavoro. - °Ist.Clinica Medica I - Università Bologna. •Cattedra Gastroenterologia - Università Chieti.

In patients with Crohn's disease (CD) the incidence of renal stone formation is about 6% before surgery and 10% after ileal resection. In this study we examined whether stone formation in CD can be accounted for by changes in main urinary risk factors. The study was performed in 9 patients with CD before and in 9 after ileal resection and right hemicolectomy with end-to-end ileotransversostomy. All subjects,on normal diet and fluid intake,were submitted to a metabolic evaluation including the measurement of creatinine,uric acid Ca,Mg,P in plasma and urine.GAGs,oxalate,citrate excretion together with volume and pH were determined in urine. Patients with CD,before surgery showed a lower excretion of Mg (54.3 ± 27.9 mg/24h;t=2.65;p< 0.01) and citrate (335 + 282 mg/24h;t=3.17;p<0.05) in comparison with healthy subjects (Mg:87 ± 35 mg/24h. Citrate:654 ± 297 mg/24h). Patients with CD displayed a significantly lower pH (p<0.02) and urinary volume (p<0.001) which induce an increase of Ca, uric acid and oxalate concentration. After surgery,urinary volume increased significantly (p<0.05) causing a decrease in all urinary parameter concentrations. Moreover,a further lowering of Mg (38.2 ± 26.5 mg/24h) and citrate excretion (242 + 273 mg/24h) was observed even if this datum did not reach a significance. In patients with CD the hypocitraturia incidence was respectively 55.6% before and 66.7% after surgery. In conclusion the main risk factors before surgery were a high urinary concentration of oxalate and uric acid as well as a low Mg and citrate excretion; while after surgery the main risk factors where the low urine pH and a reduced urinary inhibitors excretion.

● Controlled Clinical Trial of Octreotide for Refractory AIDS-Associated Diarrhea.
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Forty-nine patients (48M, 1 F) with profuse AIDS-related diarrhea were treated in an open-label multicenter controlled clinical trial with subcutaneous octreotide. Patients (mean ± SEM age 36.4± 1.1 yrs.) were known HIV+ for 9.6±1.3 mos. and had severe diarrhea (≥ 500 ml stool/day) for 10±1.1 mos. despite maximal tolerable conventional medical therapy. All had thorough clinical evaluation (including multiple stool analyses, endoscopy with small bowel biopsies and short colonoscopy) to exclude any treatable pathogens and were hospitalized on metabolic research wards for 17 days. Initial 3 day stool collections documented 6.9±.5 stools/day with 1654±189 ml stool/day. Profound steatorrhea (74±14.8 gms./72 hr) was noted on initial stool analyses while patients were maintained on a monitored fat intake. During 14 days of inpatient octreotide administration (50 ug q8 hrs. for 3 days, then 100 ug, 250 ug, and 500 ug, q8 hrs. for 3 days each if no response to prior dose) 24 hr. stool frequency and 24 hr. stool volumes decreased significantly for the entire group (stool frequency 6.9±.5 vs. 4.2±.4 stools/day [p < .00001 by paired T-test], stool volume 1654±189 vs. 1094±167 ml/day [p < .0001]). During the first 14 days of inpatient observation, there were 4 "full responders" (stools ≤ 250 ml/day), and 13 "partial responders" (stools < 50% of initial daily volume) for an overall response rate of 34.7%. Drug withdrawal resulted in a prompt return of diarrhea in patients who had previously responded. Octreotide may represent a promising new therapy in selected patients with AIDS-related diarrhea.

A SIMPLE RADIOLOGIC METHOD TO ESTIMATE THE QUANTITY OF BOWEL GAS. **T.N.Chami, M.M.Schuster, M.E.Bohlman, T.J.Pulliam, N.Kamal, W.E.Whitehead. Johns Hopkins Univ Sch of Med & Francis Scott Key Med Center, Baltimore, Maryland, 21224.**

Irritable bowel syndrome (IBS) patients frequently complain of bloating and abdominal pain. However, few and complicated attempts have been made to objectively measure intestinal gas volume. Methods: To quantify bowel gas, 55 abdominal x-rays (AXR) from 20 constipation-predominant IBS patients and one AXR from each of 11 healthy controls were examined. Sixteen patients had at least one pair of AXR 2 days apart. After masking ID plates and coding randomly, one copy of each constipated patient's AXR was given to a gastroenterologist and the other to a radiologist with instructions to outline the intestinal gas bubbles. Areas of gas bubbles were measured with a computer digitizing board (Jandel Sigma Scan TM). Bowel gas areas (BGA) on each AXR were compared between evaluators by correlation coefficients. Additionally, 5 pairs of supine-erect AXRs of 5 randomly selected emergency room patients were evaluated to determine whether change in position makes a difference in BGA. Results: The two evaluators agreed well on BGA (correlation of .95). BGA was lower in controls (69.66±26.64 cm^2) than in constipated patients (135.52±75.05, p<.02). The variation in BGA within patients was less than the variation between patients. Change in BGA within 2 days did not correlate with changes in symptom ratings for bloating (r= -.32), flatus (r=.04), or abdominal pain (r=.19). BGA was significantly greater in supine films (233.29±92.31 cm^2) than upright films (139.62±89.72 cm^2, p<.005). Conclusions: (1) Two readers can agree on amount of bowel gas in AXR indicating that this is a reliable method for assessing bowel gas. (2) BGA is higher in constipation-predominant IBS patients than controls. (3) There are individual differences in the range of BGA. (4) There is no correlation between change in BGA and change in IBS patients' subjective symptoms. (5) The consistent difference between BGA in supine vs erect films suggests that the position of the patient must be standardized and that a 3-dimensional technique (i.e., CT scan) would provide a more accurate method of quantifying bowel gas than AXR. (Supported by grants DK31369 and MH00133.)

● REDUCTION OF BILE ACID-MEDIATED INTESTINAL VASCULAR INJURY BY 16,16-DIMETHYL PROSTAGLANDIN E_2. K Chang, R.A. Erickson, K. Thapar, E. Lifrak, N. Rivera. Dept. of Medicine, DVA Medical Center, Long Beach and University of California, Irvine.

A number of investigators suggest that the primary mechanism of gastric mucosal prostaglandin-protection is at the level of the mucosal blood vessel. Whether prostaglandin causes vascular protection in bile acid-mediated injury of the intestinal mucosa is unknown.

METHODS: To test this 250-400 g pentobarbital-anesthetized male Sprague-Dawley rats were given 50 mg/kg FITC-dextran 70,000 through a femoral vein catheter. 65 cm of proximal intestine was then perfused in vivo at 1 ml/min in a single-pass fashion with an isotonic, pH 7.4 buffer containing ^{3}H-water and ^{14}C-dextran. 7 rats received 5 ug/kg 16,16-dimethyl prostaglandin E_2 (dmPGE$_2$) i.v. and 7 received vehicle after a 30 min baseline perfusion. 15 min later, intestinal injury was induced by adding 5 mM chenodeoxycholic acid (CDCA) to the perfusate for the next 45 min. The intestinal effluent was collected at 5 min intervals for measurement of sodium, chloride, ^{3}H-water, ^{14}C-dextran and FITC-dextran. Clearance of FITC-dextran from the blood to the intestinal lumen was calculated by measuring blood FITC-dextran levels every 20 min throughout the perfusion. All rats were pretreated with 10 mg/kg indomethacin i.p. one hour before anesthesia to reduce the effect of endogenous prostaglandin production. After perfusion, mucosal injury was measured morphologically using computerized image analysis of histologic intestinal samples.

RESULTS: Morphologic superficial villus injury caused by CDCA was not affected by i.v. dmPGE$_2$; however, the CDCA-induced efflux of FITC-dextran from the intestinal vessels to the intestinal lumen was significantly reduced by dmPGE$_2$ pretreatment. DmPGE$_2$ also reduced the net secretion of sodium and chloride caused by CDCA.

FITC-Dextran Clearance Blood –> Lumen (ul blood/min/cm x 1000)

Time after CDCA	15	20	25	30	35	40	45
Vehicle	16	30	54	89	149	200	191
DmPGE$_2$	16	21	30 a	38 b	49 c	63 d	88 d

a= p<.01, b= p<.025, c= p<.05, d= p<.005 by ANOVA

CONCLUSIONS: As evidenced by decreased intestinal leakage of intravascular FITC-dextran, this study suggests that dmPGE$_2$ significantly reduces bile acid-mediated intestinal vascular injury. This finding supports vascular protection being a generalized mechanism of prostaglandin protection in the gastrointestinal mucosa.